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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/990,438	11/14/2001	Avi J. Ashkenazi	10466/201	2374
35489	7590	11/09/2004	EXAMINER	
HELLER EHRMAN WHITE & MCAULIFFE LLP 275 MIDDLEFIELD ROAD MENLO PARK, CO 94025-3506			KAUFMAN, CLAIRE M	
			ART UNIT	PAPER NUMBER
			1646	

DATE MAILED: 11/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/990,438	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Claire M Kaufman	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 August 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 124, 125 and 129-131 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 124, 125 and 129-131 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date: _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>8/20/04</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Response to Arguments

The rejections of claims under 35 USC 112, second paragraph and first paragraph-written description, are withdrawn in view of the amendment to the claims or moot in view of cancellation of the claims. Note a new rejection appears below under 35 UCS 112, second paragraph.

The rejection of claims under 35 USC 102 is withdrawn in view of the cancellation of the claims. As discussed in the *Claim Interpretation* section below, the GenBank reference cannot properly be applied as art to the currently pending claims.

Rejections of cancelled claims are moot.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Interpretation

For claims drawn to "An isolated polypeptide comprising an amino acid sequence" of SEQ ID NO:33 (Claim 124), the polypeptide may include additional amino acid sequence on either end of said sequence (e.g., p.304, lines 19-25). With this interpretation, the splice variant of GenBank AB011112.1 which encodes a polypeptide identical to SEQ ID NO:33 of the instant application with the exception of a 30 amino acid insert and is encoded by a nucleic acid identical to SEQ ID NO:32 with the exception of a 90 nucleotide insert, would not qualify as a polypeptide comprising the polypeptide SEQ ID NO:33. For this reason, the GenBank reference is not being applied to claim 124 or dependent claims. If Applicants feel this interpretation is in error, this should be stated in the response to this office action and will not preclude the next Office action from being made final since the issue was raised here.

Response to Amendment

The Declarations of Drs. Ashkenzi and Polarkis under 37 CFR 1.132 filed 08/20/04 is insufficient to overcome the rejection of claims 124, 125 and 129-131 based upon 35 USC 101/112, first paragraph, as set forth in the last Office action because: they are not sufficient to

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overcome the rejections for the reasons discussed in response under the rejections below. While the Declaration of Ashkenazi shows that "real-time PCR" is a reliable means of determining gene copy number in cells or tissues, there are utility and enablement issues of protein vs. DNA not resolved by the declaration that require the rejection to be maintained. While statements are made in the Polarkis Declaration about correspondence of DNA amplification and encoded polypeptide increase in particular cell types based on antibody binding studies, there is evidence on the record to refute the generalization of correspondence and there is no evidence accompanying the declaration to support the correspondence. The utility and enablement for the claims are further discussed under the appropriate section for the rejections below.

Claim Rejections - 35 USC § 101/112, First Paragraph

Claims 124, 125 and 129-131 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth in the previous Office action.

Claims 124, 125 and 129-131 remain also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for the reasons set forth in the previous Office action.

Applicant argues that gene amplification, which is well described in the specification, is a patentable utility for the PRO290 protein. The argument has been fully considered, but is not persuasive. As stated in the previous Office action (p. 3, lines 13-21):

Even though the nucleic acid has utility as a probe for screening for lung tumor cells, the encoded polypeptide has no such utility since there is no reason to suspect that there is alteration of polypeptide sequence or amount in lung tumor versus normal tissue. Even if the DNA has utility as a lung tumor marker, the encoded protein does not have utility because it is not known what the protein does or if the level of PRO290 protein in lung tumors corresponds to nucleic acid transcript level, i.e., if an increased gene amplification in lung tumors corresponds to an increased amount of expressed protein. It does not necessary follow that an increase in gene copy

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number results in increased gene expression and increased protein expression, such that the polypeptide would be useful diagnostically or as a target for cancer drug development.

Gene amplification alone does not provide utility for an encoded polypeptide without a further showing of a reasonable expectation that the polypeptide itself has a significantly elevated or decreased level associated with a tumor, disease, *etc.*

Applicant argues that the data of Pennica et al. about the correlation or lack thereof between gene amplification and WISP protein expression is not generalizable. The argument has been fully considered, but is not persuasive. While Pennica et al. alone does not support a lack of correlation, the references relied upon together do. Pennica et al. show an example of the unpredictability correlating gene amplification and protein level. Haynes et al. found a “general trend” but no significant correlation between nucleic acid level and translation. It is maintained that the correlation between each gene and corresponding protein in tumors is unpredictable, and Applicants have presented no showing that would allow the skilled artisan to conclude that it is more likely than not that the amount of *both* the PRO290 encoding gene and protein are increased in squamous cell-type lung carcinomas (SqCCa).

Applicant argues that the Haynes et al. publication does not support the rejection. Applicant characterizes Haynes et al. as teaching concluding there is a general trend but no strong correlation between polypeptide expression level and transcript level. Applicant criticizes Haynes et al. for being directed to a study of yeast polypeptides. Applicant further characterizes Haynes et al.’s conclusions as showing that there is a positive correlation between transcript and polypeptide for most of the 80 yeast polypeptides studied, but the correlation is not linear and thus one cannot accurately predict polypeptide levels from mRNA levels. Applicant stresses that very few data points scattered away from the expected normal or showed a lack of correlation between mRNA and polypeptide. Applicant concludes that Haynes et al. show that it is more likely than not that a positive correlation exists between mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. In the instant case, the specification provides data showing a very small increase in **DNA** copy number, approximately **2-fold**, in a few tumor samples for PRO290. There is no evidence regarding whether or not the PRO290 **mRNA** or **polypeptide** levels are also increased in these tumor samples. Since the instant claims

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are directed to and PRO290 **polypeptide**, it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased in mRNA and polypeptide levels. Pennica et al. was cited as evidence showing a lack of correlation between gene (DNA) amplification and elevated mRNA levels. Additionally, Konopka et al. (PNAS, 83:4049-52. 1986) states that, "Protein expression is not related to amplification of the *abl* gene but to variation in the level of bcr-*abl* mRNA production from a single Ph1 template" (see abstract). Konopka et al. also provide evidence showing lack of correlation between gene amplification and increased polypeptide levels. Haynes et al. was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels, and that variances as much as 40-fold or even 50-fold were not uncommon (p. 1863). Haynes et al. used yeast as an art-accepted model for eukaryotic systems. Given how small the DNA copy number of PRO290 increased, and the evidence provided by Haynes et al., Pennica et al. and Konopka et al., it was clear that one skilled in the art would not assume that a small increase in gene copy number would correlate with significantly increased mRNA or polypeptide levels. One skilled in the art would do further research to determine whether or not the PRO290 polypeptide levels increased significantly in the tumor samples. Such further research requirements makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Applicant refers to four additional articles (Hanna et al., Orntoft et al., Hyman et al. and Pollack et al.) as providing evidence that gene amplification generally results in elevated levels of the encoded polypeptide. Hanna et al. does not discuss protein levels, but correlates cancer

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prospects with amplification of certain genes. Applicant characterizes Orntoft et al. as teaching in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Applicant characterizes Hyman et al. as providing evidence of a prominent global influence of copy number changes on gene expression levels. Applicant characterizes Pollack et al. as teaching that 62% of highly amplified genes show moderately or highly elevated expression and that, on average, a 2-fold change in DNA copy number is associated with a 1.5-fold change in mRNA levels. The arguments relating to these references has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region (see for example, p 44, last paragraph of col. 1). Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO290 in the instant specification. That is, it is not clear whether or not PRO290 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Hyman et al. used the same CGH approach in their research. Less than half (44%) of highly amplified genes showed mRNA overexpression (abstract). Polypeptide levels were not investigated. Therefore, Hyman et al. also do not support utility of the claimed polypeptides. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. did not investigate polypeptide levels. Pollack et al. also noted contradictory results found by another research group, noting that, "Alternatively, the contrasting findings for amplified genes may represent real biological differences between breast and metastatic colon tumors; resolution of this issue will require further studies" (p. 12968, end of first paragraph). This leads again to the issue of unpredictability. Therefore, Pollack et al. also do not support the asserted utility of the claimed invention. Importantly, none of the later three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the

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development of potential cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. While the research of Hanna et al. was directed to identifying nucleic acid probes for cancer diagnostics, there was no support for polypeptides as diagnostic agents. Accordingly, the specification's assertions that the claimed PRO290 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Applicant's arguments directed to the Polakis declaration filed under 37 CFR 1.132 have been fully considered but are not found to be persuasive for the following reasons. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive. First, it is important to note that the instant specification provides no information regarding increased mRNA levels of PRO290 in tumor samples relevant to normal samples. Only gene amplification data was presented. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. There is no evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or

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less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants argue the declaration filed by Dr. Ashkenazi under 35 USC 1.132 supports the gene amplification data in the present application because "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product," that in itself provides important information for cancer diagnosis and treatment. There is no evidence that clinicians use information about a gene product *not* being overexpressed as a basis for deciding to not treat a patient with an agent that targets that gene product. This is a hypothetical utility not disclosed in the specification.

For all of these reasons, the rejections are maintained.

NEW:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 124 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As amended, claim 124 recites the limitation "the nucleic acid encoding" in the second to last line. There is insufficient antecedent basis for this limitation in the claim. It is unclear if "the nucleic acid" refers to "the cDNA" in (b) or another unspecified nucleic acid.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

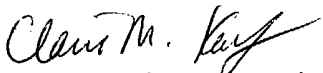
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday and Thursday from 8:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (703) 872-9306. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. **Please** advise the examiner at the telephone number above before facsimile transmission.

Claire M. Kaufman, Ph.D.


Patent Examiner, Art Unit 1646

November 8, 2004


LORRAINE SPECTOR
PRIMARY EXAMINER